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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/709,577	05/14/2004	Itzhak Bentwich	050992.0202.02USCP	3576

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/709,577	BENTWICH ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27,29-31 and 33* is/are pending in the application.

4a) Of the above claim(s) *26,29,30 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/20/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/20/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 3/20/08, claims 25-27, 29-31, and 33 are pending in the application. Claims 26, 29, and 33 remain withdrawn. Claim 30 is hereby withdrawn for the following reasons. Newly submitted claim 30, drawn to SEQ ID NO:7014085, is directed to an invention that is independent or distinct from the invention originally claimed, drawn to SEQ ID NO:7002375. As shown below (see extracts from the sequence listing), SEQ ID NO:7014085 is structurally distinct from SEQ ID NO:7002375. Accordingly, the inventions of claims 25 and 30 have materially different designs. For the same reasons, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. See MPEP § 806.05(j). It would be a burden to search each of these sequences in claims 25 and 30 in the same application given the complex nature of sequence searches in terms of computer time and analysis and since each sequence would require a separate search and analysis of the patent and non-patent literature. Restriction to one sequence is proper therefore.

Since applicant has received an action on the merits for the originally presented invention---isolated nucleic acids consisting of, equivalent to, or complementary to SEQ ID NO:7002375---this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 30 and any claim dependent therefrom is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim 27, drawn to SEQ ID NO:6816665, is considered to link the inventions of claims 25 and 30. The restriction requirement between the linked inventions is **subject to** the nonallowance of the linking claim(s). Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

<210> 7002375
<211> 22
<212> DNA
<213> Homo sapiens

<400> 7002375
acatacacgg gaaacctctt tt 22

search version:
acatacacgggaaacctctttt

<210> 6816665
<211> 81
<212> DNA
<213> Homo sapiens

<400> 6816665
gatactcgaa ggagaggttg tccgtgttgt cttctcttta tttatgatga aacatacacg 60

ggaaacctct tttttagtat c 81

search version:
gatactcgaaggagaggttgtccgtgttgtcttctctttatttatgatgaaacatacacgggaaacctctttttttagtatc

<210> 7014085
<211> 22
<212> DNA
<213> Homo sapiens

<400> 7014085
aaggagaggt tgtccgtgtt gt 22

search version:
aaggagaggttgtccgtgttgt

Altogether, then, claims 26, 29, 30, and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 25, 27, and 31 are under consideration.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Election/Restrictions/Status/Amendment/Claims

To review, in the reply filed on 7/2/07 Applicant elected without traverse Group I, claims 25-32, drawn to an isolated nucleic acid comprising at least 16 nucleotides of SEQ ID NO:10,068,310. Applicant further elected without traverse SEQ ID NO:7,002,375. Applicant stated SEQ ID NO: 7,002,375 corresponds to target gene ACTN4, having GenBank Accession No. NM_004924.

Sequence listing---Notice to Comply

While the previous Action stated the objection to the disclosure because of an invalid sequence listing had been withdrawn, the Examiner has been informed by the Office's Electronic Information Center, which uploads sequence listings into the Supplemental Complex Repository for Examiners (SCORE), that the computer readable form (CRF) of the sequence listing submitted by Applicant on or about 3/21/07 is defective because the sequence listing does not comply with 37 CFR 1.824(a)(1), which states "The computer readable form shall contain a single "Sequence Listing" as either a diskette, series of diskettes, or other permissible media outlined in paragraph (c) of this section" (underline added).

In the instant case, the CRF submitted by Applicant on or about 3/21/07 comprises at least 51 separate sequence listing text files. Pursuant to 37 CFR 1.824(a)(1), the CRF must be a single file, though the file may span multiple disks. Thus, this application, which contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), remains non-compliant with the requirements of 37 CFR 1.821 through 1.825. For submission via EFS, Applicant should contact the Electronic Business Center (EBC) for more information. Alternatively, or in addition,

Applicant may contact the STIC Systems Branch Help Desk at 571-272-2510, regarding correction of the 3/21/07 EFS submission.

Specification

The specification is further objected to under 35 U.S.C. 132(a) because the amendment to the sequence listing filed 3/21/07 introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is SEQ ID NO:10,068,310.

As explained in an earlier action, SEQ ID NO:10,068,310 is not supported by the disclosure as originally filed. Because the sequence listing is considered to be a part of the disclosure amendments to the sequence listing adding new sequences not supported by the application are considered to represent new matter.

In the instant case, Applicant has previously pointed to Table 10, lines 345905-345934, Table 1, and Table 2, which tables are contained on compact discs submitted with the original application. Applicant describes how individual sequences set forth therein are related to one another, stating, for example, that the sequences set forth in Tables 1 and 2 together make up a precursor sequence referred to as GR5737, which applicant claims represents SEQ ID NO:10,068,310. Table 10 states GR5737 is an RNA precursor sequence that is processed into at least 82 separate RNA precursor sequences. Applicant submits that, altogether, the information set forth in the separate tables establishes possession of not only the 44,000-nucleotide sequence corresponding to SEQ ID NO:10,068,310, but all nucleic acids of 16-120 nts in length identical and complementary to this sequence, as well as RNA equivalents thereof.

However, Applicant's explanation of how the individual sequences may be cobbled together to produce a super sequence cannot supplement or replace the original disclosure. What is needed is explicit, implicit, or inherent description of the claimed nucleic acid sequence itself in the specification as originially filed.

To start, SEQ ID NO:10,068,310 does not appear to be disclosed in the original sequence listing, the basis for which would appear to be mega tables 1-15. A complete sequence listing was not submitted until 3/21/07, after filing. This sequence listing adds SEQ ID NO:10,068,310, which does not appear in the application as originally filed.

Support is not readily found in either the 245-page specification or in any of the mega tables 1-15 submitted with the application (MPEP 2164.04).

Furthermore, it is unclear how one of skill would clearly recognize SEQ ID NO:10,068,310 from the disclosure cited in Tables 1, 2, and 10. For example, each of the 82 RNA products derived from GR5737 according to Table 10 are not found in tables 1 and 2, and it is unclear how one of skill would recognize the relationship between GR5737 and the sequences set forth in tables 1 and 2 from the original disclosure.

Thus, a review of the specification fails to find clear, antecedent support for SEQ ID NO:10,068,310.

Accordingly, an amendment to the sequence listing, i.e., disclosure, adding SEQ ID NO:10,068,310 is considered to constitute new matter.

Information Disclosure Statement

The information disclosure statement filed 3/20/08 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the title of each publication listed in the information disclosure has not been provided. See 37 CFR 1.98(b)(5).

It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 101 and 112, First Paragraph—maintained

Claims 25, 27, and 31 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by a credible asserted utility.

Response to Arguments

To be clear, the rejection herein and going forward is based primarily on a lack of credible asserted utility.

SEQ ID NO:7002375 is said by Applicant to regulate the expression of MAPKAPK2. In this respect, the asserted utillity is specific and substantial. However, the assertion is not credible, as previously explained. There is substantial evidence to indicate that, at the time of filing, one of skill would have had reason to doubt the objective truth of these statements, given the proposed target was bioinformatically predicted, the accuracy and/or false positive rate of the

bioinformatic prediction method was and remains unknown, and given that no experimental data is available to confirm the predicted activity. The claimed sequences are significantly less than 100% complementary to the predicted targets, and, operate, according to the applicant, by standard miRNA-guided mechanism to regulate expression. However, there is no evidence in the prior art or application to show that each and every miRNA-like hairpin predicted by the instant algorithm in fact regulates expression of a gene. Indeed, miRNA-like, non-translated hairpin RNAs may have any number of different biological activities in the cell, known or yet-to-be discovered. The fact that several miRNAs have been biologically validated using actual in vitro assay does not necessarily mean that each miRNA-like hairpin and proposed maturation product thereof regulates a gene. This would appear to be a primary assumption of the instant invention.

Applicant's arguments and the Declaration under 37 CFR 1.132 filed 3/20/08 have been fully considered but are not persuasive for the reasons enumerated below.

In previous Office Actions, the Office has presented evidence suggesting there would have been reason at the time of filing to doubt the objective truth of the asserted utility. Further evidence is presented herein.

In brief, the instant application claims bioinformatically predicted preprocessed and mature miRNA sequences corresponding to SEQ ID NO:6816665 and 7002375, respectively. Applicant asserts one of skill would more likely than not conclude the claimed nucleic acids may be used to modulate the expression of a specific gene. Specific and substantial utility is thereby asserted based on bioinformatic data. The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function. Function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin

sequences and mature miRNAs derived therefrom by Dicer-catalyzed processing, which information is mined from raw genomic sequences.

At issue, then, is whether one of skill would more likely than not believe the nucleic acids predicted by Applicant's algorithm, such as the sequences now claimed, would have the specific and substantial utility predicted by the program.

1. The Declaration under 37 CFR 1.132 filed 3/20/08 has been fully considered, but is insufficient to overcome the rejection of claims in view of the totality of the evidence in the pre- and post-filing art. Though made by a proclaimed expert in the art, and containing sound scientific reasoning, the Declaration represents nothing more than an opinion. While the declaration quantifies the effectiveness of other miRNA prediction algorithms, the declaration does not directly quantify the accuracy and/or false positive/false negative rate of the Inventor's algorithm, the program in question. Instead, the Declaration attempts to show the veracity of the instant prediction software by comparison to related prediction programs. Though unclear from the declaration, the assertion appears to be the instant algorithm is at least as effective as prior art algorithms. However, post-filing art (cited below) indicates it is difficult if not impossible to compare different algorithms without comparing their output using a common dataset, which does not appear to have been done here. The Declaration provides no experimental evidence validating either the predictive quality of the instant algorithm or the utility of the instantly claimed sequences. Such evidence if collected in a statistically relevant manner would be indicative of the accuracy of the algorithm. While declarant describes the accuracy of related miRNA prediction

programs in detail, there is no discussion of the accuracy of the instant miRNA prediction program, which is the subject of this application. The determinative factor is the accuracy and false positive rates associated with the program used to predict the instantly claimed miRNAs. Comparing the performance of this program to any other is difficult when the programs have not been run on identical data sets and when there is no objective experimental data substantiate the claims of the declarant.

2. The Declaration similarly fails to address the utility of SEQ ID NO:6816665 or the isolated nucleic acids complementary to either SEQ ID NO: 6816665 or 7002375, much less sequences that are only 80% identical to either the sequences themselves or their complements. The only perceived utility of the complements would be to either inhibit or detect the bioinformatically predicted miRNAs themselves. However, there is absolutely no evidence, beyond the algorithm, that the claimed miRNAs are biologically active in any manner, or even expressed by any cell. Thus, the complements lack both substantial and credible utility since there is no evidence the targets of these complements have any utility or that any information of immediate, real-world value could be obtained from the use of sequences complementary to the claimed miRNAs. As for sequences less than 100% complementary to the claimed nucleic acids, there is no evidence beyond bare assertion that any of these sequences would have any utility, specific, substantial or credible. Here, the utility is unknown and there is no assurance any would ever be found.
3. The question remains whether the bioinformatically predicted miRNAs now claimed would, more likely than not, have the utility asserted. The answer lies in the

predictive quality of the program used to identify the miRNAs and their target sites. A quantifiable value is not readily apparent to the Examiner from the facts of record. Indeed, the Examiner is unable to find any disclosure by the inventor either in the instant application or in the pre- or post-filing art clearly articulating the sensitivity or false positive rate of the instant algorithm. A simple statement supported by actual experimental evidence, showing the algorithm correctly predicts an miRNA and its activity more than half of the time and has an acceptable false positive rate would be sufficient to overcome the instant rejection.

4. Currently, however, neither the Declaration nor the specification addresses this question directly or completely. Accuracy would depend on several factors, including but not limited to the accuracy of the HAIRPIN DETECTOR and the accuracy of the DICER-CUT LOCATION DETECTOR. At paragraph 407, the specification states the algorithm has the ability to detect real target genes with 47% accuracy. This would not appear to meet the credibility standard of more likely than not. The predicted miRNA may hybridize to countless numbers of different genes. The proposed target is simply a starting point for further research.
5. Further, it would appear from the teachings in the specification that multiple determinants govern the selection process.
6. Critical to the determination of whether the asserted utility is credible is the false positive rate of the instant prediction program. This information is not found in the instant application. Comparative algorithms used in the art are said to have false positive rates of between 22% and 39%. See Bentwich et al. (2005) *FEBS Lett.*

579:5904-5910, page 5907; and the Declaration, Point 4. See also Martin et al. (2007) *J. Biosci.* 32:1049-1052 at page 1049, 4th full paragraph.

7. Martin et al. (2007) *J. Biosci.* 32:1049-1052, reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.
8. The post-filing art suggests that it is difficult to estimate the true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known. See Maziere et al. (2007) *Drug Discovery Today* 12:452-458, page 457. Maziere et al. in their article entitled "Prediction of miRNA Targets," further state that comparison of miRNA prediction efficiencies among different programs is not currently possible because many of the programs are not available for download and use on a common dataset; thus, Maziere et al. cast doubt on the reliability of the statements made in the Declaration, comparing similar programs to that used by the

Inventor. Again, no evidence has been presented by Declarant directly comparing the output of the instant algorithm with the other cited programs when presented with a common dataset. Thus, there is no objective evidence to corroborate Declarant's opinion.

9. Smalheiser et al. (2006) *Methods Mol. Biol.* 342:115-127 in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential importance of mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential mRNA targets from being effectively silenced by the RNA-induced silencing complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs interact with their targets via "short seeds," complementary regions of 6-8 nucleotides, but, instead, may interact via "long" seeds and perfect matches (page 115-6), and because new miRNAs are constantly being discovered this list of binding determinants may not be complete.
10. Thus, multiple factors are involved in miRNA-target binding and recognition.
11. Thus, in view of the totality of the evidence, one of skill would have reason to doubt the objective truth of the asserted utility. While the instant algorithm provides a list of putative miRNAs and corresponding target sites, there is reason to question whether

the bioinformatic algorithm used to produce this list correctly identifies an miRNA and its function (i.e., at least one biological function) with minimally acceptable false positive and false negative rates such that one of skill would believe the miRNA would, more likely than not, inhibit the gene predicted by the software. Without experimental validation or any verifiable evidence of the accuracy and error rates of the instant program, and in view of the state of the art at the time of invention, one of skill would reasonably question the certainty of the prediction at the time of filing.

12. The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

***

Claims 25, 27, and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner, AU 1635
June 6, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635